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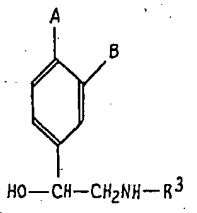
(54) α-AMINOMETHYLBENZYL ALCOHOL DERIVATIVES

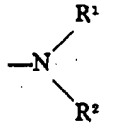
(71) We, YAMANOUCHI PHARMACEUTICAL CO. LTD., a Japanese Company of No. 5—1 Nihonbashi Honcho 2-chome, Chuo-ku, Tokyo, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates generally to α-aminomethylbenzyl alcohol derivatives and more particularly it relates to α-aminomethylbenzyl alcohol derivatives represented by the general formula I



I

wherein one of A and B represents a hydrogen atom or a hydroxyl group while the other represents a



group (in which R^1, which is different from R^2, represents a hydrogen atom or an alkyl group and R^2 represents a hydrogen atom or a —CO—R^4 group wherein R^4 represents a hydrogen atom or an alkyl group which may be substituted by a hydroxyl group, an alkoxyl group or an acylamino group) and R_3 represents an alkyl group other than a methyl group or a phenylalkyl group which may be substituted by a hydroxyl group, an alkyl group, an alkoxyl group, or an acylamino group.

Compounds of this invention have utility as β-adrenergic stimulants and thus have great activity on respiratory smooth muscle and are suitable as bronchodilating agents.

As α-alkylaminomethylbenzyl alcohol derivatives, there are known, for example, 3-amino - 4 - hydroxy - α - isopropylaminomethylbenzyl alcohol (see, Dutch Patent No. 85,197; "Chemical Abstract", *52*, 11121d (1958)), 3 - ethoxycarbonylamino - 4 - hydroxy - α - isopropylaminomethylbenzyl alcohol (see, Belgian Patent No. 765,986), and α-(isopropylaminomethyl) - 4 - hydroxy - 3-ureidobenzyl alcohol (see, Published Japanese Patent Application No. 2674/'71).

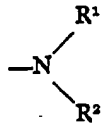
Compounds of this invention have, however, more excellent bronchodilator activity than those known compounds.

In the formula I representing the compounds of this invention, examples of the alkyl group represented by the substituents R^1, R^3, and R^4 include a methyl group, an ethyl group, a propyl group, an isopropyl group, a *n*-butyl group, a tert-butyl group, a 1,3-dimethylbutyl group, a 1,3-dimethylpentyl

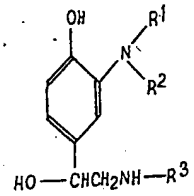
group, a 2,3-dimethylbutyl group, and a 2,3,3 - trimethylbutyl group, examples of the alkoxyl group which may be present in the substituents R^3 and R^4 include a methoxy group, an ethoxy group, an isopropoxy group, a tert-butoxy group, and a neopentyloxy group, and examples of the acylamino group which may be present in the substituents R^3 and R^4 include an acetamido group, a propionamido group, a benzamido group, and a pyridinecarbonylamino group.

The particularly useful compounds of this invention are 3-formamido-4-hydroxy-α-[N-(1 - methyl - 2 - p - hydroxyphenylethyl)-aminomethyl]benzyl alcohol, 3-formamido-4-hydroxy - α - [N - (1 - methyl - 2 - p - methoxyphenylethyl)aminomethyl]benzyl alcohol, and 4 - hydroxy - 3 - methylamino - α - (N-tert-butylaminomethyl)benzyl alcohol.

When A in formula I is a hydroxyl group and B is the

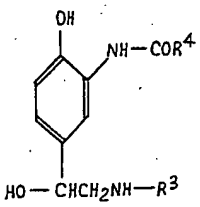


group, the compounds of this invention are represented by the formula I'



I'

wherein R^1, R^2, and R^3 have the same significance as in the formula I. More specifically the formula I' includes the following three formulae;



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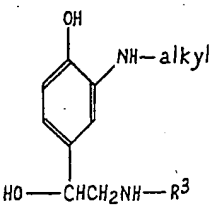

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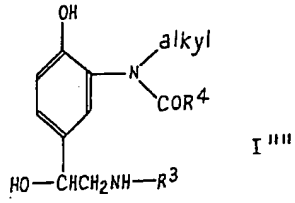


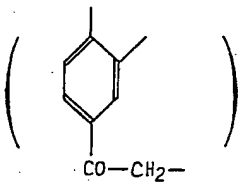
I''''

in the above formulae, R^3 and R^4 have the same significance as in the formula I.

The compounds of this invention may be prepared by catalytic reduction of the appropriate starting materials or salts thereof in a solvent such as ethanol, isopropanol or ethyl acetate at normal temperature or an elevated temperature, under a normal pressure or a high pressure, in the presence of a catalyst such as palladium, or platinum using a conventional process.

As starting materials for preparing the desired compounds by reduction, compounds having one or more hydrogen atoms on the amino group or having a hydroxyl group may need protection by a group capable of being easily released by reduction, such as a benzyl group, a benzyloxycarbonyl group, or a p-nitrobenzyloxycarbonyl group.

Furthermore, the starting material for the desired compound which has a secondary hydroxyl group bonded to the benzene ring, may be the compound having a carbonyl group at the position



Practical examples of starting materials for the compounds of this invention are as follows:

3 - formamido - 4 - benzyloxy - α - (N-benzyl - N - isopropylaminomethyl)benzyl alcohol,

3 - acetamido - 4 - benzyloxy - α - (*t*-butylaminomethyl)benzyl alcohol,

3 - propionamido - 4 - hydroxy - α - (N-benzyl - N - *n* - butylaminomethyl)benzyl alcohol,

3 - nicotinoylamino - 4 - benzyloxy - α-[N - benzyl - N - (2,3 - dimethylbutyl)-amino]acetophenone,

3 - formamido - 4 - benzyloxy - α - (3-*p* - hydroxyphenyl - 1 - methylpropylamino)-acetophenone,

3 - acetamido - 4 - hydroxy - α - [N-benzyl - N - (4 - phenyl - 2,3,3 - trimethylbutyl)amino]acetophenone,

3 - formamido - 4 - benzyloxy - α - [N-benzyl - N - (1 - methyl - 2 - *p* - hydroxy-

phenylethyl)aminomethyl]benzyl alcohol,

3 - acetamido - 4 - benzyloxy - α - [N-(1 - methyl - 3 - *m* - tolylpropyl)aminomethyl]benzyl alcohol,

3 - benzyloxyacetamido - 4 - hydroxy - α-[N - benzyl - N - (1 - ethyl - 2 - p - methoxyphenylpropyl)amino]acetophenone,

3 - (3 - benzyloxypropionamido) - 4-benzyloxycarbonyloxy - α - [N - (1 - methyl-2 - *m* - acetamidophenyl)amino]acetophenone,

3 - (2 - acetamidopropoamido) - 4-hydroxy - α - [N - benzyl - N - (1 - methyl-3-*o*-tolylpropyl)amino]acetophenone,

3 - butyrylamino - 4 - hydroxy - α - [N-(*o* - methyl - *m* - ethoxyphenylpropyl)-amino]acetophenone,

3 - formylamino - 4 - benzyloxy - α - [N-benzyl - N - 1,1 - dimethyl - 2 - *p* - hydroxyphenylethyl)aminomethyl]benzyl alcohol,

3 - acetamido - 4 - benzyloxy - α - [N-benzyl - N - (*o* - methyl - m - acetamidophenylethyl)aminomethyl]benzyl alcohol,

3 - formamido - 4 - hydroxy - α - [N-benzyl - N - (1 - ethyl - 2 - *p* - hydroxyphenylethyl)aminomethyl]benzyl alcohol,

3 - formamido - 4 - benzyloxy - α - [N-benzyl - N - (1 - methyl - 2 - *p* - acetamidophenylethyl)aminomethylbenzyl alcohol,

3 - benzyloxyacetamido - 4 - hydroxy - α-[N - benzyl - N - (1 - methyl - 2 - *p*-propoxyphenylethyl)amino]acetophenone,

3 - acetamidopropioamido - 4 - benzyloxy-α - [N - benzyl - N - (1 - methyl - 2 - *p*-ethoxyphenylethyl)aminomethyl]benzyl alcohol,

3 - formamido - α - (N - benzyl - N-isopropylaminomethyl)benzyl alcohol,

3 - formamido - α - (N - benzyl - N - *t*-butylaminomethyl)acetophenone.

When the group R^3 or R^4 of a starting material for a compound of this invention contains a hydroxyl group which has been protected by for example a benzyl group or a benzyloxycarbonyl group, the protecting group is released to give the free hydroxyl groups during the aforesaid reduction.

The desired product of formula I thus obtained can be isolated and purified by an ordinary chemical operation.

Because a compound of formula I of this invention has at least one asymmetric carbon atom, the invention includes all the possible optically active forms and racemic mixtures. A racemic mixture may be resolved by a known method such as, for example, forming an addition salt with an optically active acid and then separating the optically active salts by fractional crystallization.

The pharmacological effects of the compounds of this invention are illustrated in the following experiments and results while comparing these with similar data in respect of known compounds.

Experimental Procedure 1.

Activity on isolated bronchial smooth muscle (*in vitro* test):

Trachea were removed from guinea pigs, cut spirally and the isolated bronchial preparation was suspended in a Mangus bath. Tyrode fluid was employed as nutrient solution and was controlled at 37° C. 10^{-5} g/ml. of histamine or methacholine chloride was added to the preparation as agonist. After the contraction of the trachea reached a plateau, the test compound shown in the table below were added cumulatively to the preparation. A dose giving 50% relaxation of the bronchial muscle was designated as ED_{50}.

Experimental Procedure II.

Experimental antiasthmatic action (*in vivo* test):

A guinea pig was placed in a 11 liter glass vessel and then a broncho-constrictor was sprayed in it by means of a nebulizer. Thus, when 0.01% histamine or methacholine chloride solution was sprayed for 10 seconds, the guinea pig showed symptoms of dyspnea. Ten mg/kg of test compound was administered orally to guinea pigs 30 minutes or 2 hours before application of the bronch-constrictor. If the guinea pig showed no dyspnoic symptoms on subsequent treatment, the sample was regarded as effective.

The results obtained in the above experiments are shown in the following table.

Test Compound	Experiment I (ED_{50}, g/ml)		Experiment II (a/b)*			
	Histamine	Methacholine chloride	Histamine		Methacholine chloride	
			30′	120′	30′	120′
Product of Ex. 5	1×10^{-9}	5×10^{-8}	5/5	3/5	4/5	1/5
,, 14	2×10^{-7}	6×10^{-6}	5/5	5/5	5/5	4/5
,, 11	9.4×10^{-10}	1.1×10^{-8}	5/5	5/5	5/5	5/5
,, 12	3.6×10^{-9}	8.4×10^{-8}	5/5	5/5	5/5	5/5
,, 26	4.6×10^{-10}	4.6×10^{-9}	5/5	5/5	5/5	5/5
Known Compounds						
A	3×10^{-7}	3×10^{-6}	3/5	2/5	5/5	3/4
B	5×10^{-6}	$>10^{-4}$	1/5	0/5	1/5	0/5
C	9×10^{-8}	$>10^{-4}$	1/5	1/5	0/5	0/5
D	10×10^{-8}	9.6×10^{-8}	5/5	5/5	5/5	5/5
E	2.7×10^{-9}	2.1×10^{-8}	5/5	5/5	5/5	5/5

: a/b = effectiveness ratio, where (a)effective number, (b) tested number.

Known compounds used above are as follows:

A: 3 - amino - 4 - hydroxy - α - isopropylaminomethyl benzyl alcohol (Dutch Patent No. 85,197).

B: 3 - ethoxycarbonylamino - 4 - hydroxy-α - isopropylaminomethyl benzyl alcohol (Belgian Patent No. 765,986).

C: 4 - hydroxy - 3 - (N′ - methylureido)-α-isopropylaminomethyl benzyl alcohol (Published Japanese Patent Application No. 2674/'71).

D: Solbutamol; 4 - hydroxy - 3 - hydroxymethyl - α - *t* - butylaminomethyl benzyl alcohol.

E: Trimetoquinol, 1 - 1 (3,4,5 - trimethoxybenzyl) - 6,7 - dihydroxyl - 1,2,3,4-tetrahydro isoquinoline hydrochloride.

From the results above, it will be clearly understood that compounds of this invention are superior to known bronchodilating agents having similar and unsimilar structures to the compounds of this invention.

Compounds of this invention may be used in various forms for cure and prevention of illnesses and in general they are used as their salts with pharmacologically acceptable acids. For example, they are used as the salts of such inorganic acids as hydrochloric acid, sulfuric acid and phosphoric acid, or organic acids such as fumaric acid, maleic acid, acetic acid, lactic acid, and citric acid.

The compounds of this invention may be administered orally or parentarally as a pharmaceutical composition with an acceptable diluent or medium. In case of oral administration they may be in the forms of sugar-coated tablets, buccals, or capsules. They may also be in the form of aerosols for inhalation. Furthermore, they may be injected subcutaneously, intramuscularly, or intravenously.

The dosage of the compounds of this invention depends upon the condition and age of patients and on the administration form but the suitable oral dosage range for an adult is 0.3—1.5 mg./day.

Reference Preparation 1.

a). In 60 ml. of chloroform was dissolved 5.4 g. of 4-benzyloxy-3-nitroacetophenone and after adding dropwise to the solution a mixture of 3.2 g. of bromine and 5 ml. of chloroform with stirring, the mixture was stirred further for 30 minutes. The reaction product was concentrated under a reduced

pressure and the crystalline residue obtained was washed with 20 ml. of benzene and dried to give 5.5 g. of 4-benzyloxy-3-nitro-α-bromoacetophenone. The product, when recrystallized from chloroform, melted at 135—136° C.

b) In 60 ml. of tetrahydrofuran was dissolved 5.3 g. of 4-benzyloxy-3-nitro-α-bromoacetophenone and after adding to the solution 4.5 g. of N-benzyl-N-isopropylamine, the mixture was stirred overnight at room temperature. After filtring off the precipitate thus formed, the filtrate was concentrated under a reduced pressure and the crystalline residue obtained was washed with ethanol to provide 5.5 g. of yellow crystals of 4 - benzyloxy - 3 - nitro - α - (N - benzyl-N-isopropylamino)acetophenone. The product, when recrystallized from ethanol, melted at 92—93° C.

c). In 35 ml. of ethanol was suspended 3.5 g. of 4-benzyloxy-3-nitro-α-(N-benzyl-N-isopropylamino)acetophenone and after adding to the suspension 0.4 g. of sodium borohydride, the mixture was stirred for 3 hours at room temperature. After distilling off ethanol from the reaction product under a reduced pressure and adding water to the residue, the product was extracted with benzene. The extract was washed with water, dried over anhydrous magnesium sulfate, and then concentrated under a reduced pressure to provide 3.4 g. of faint-yellow crystals of 4-benzyloxy-3-nitro-α-(N-benzyl - N - isopropylaminomethyl)benzyl alcohol. The product, when recrystallized from ethanol, melted at 97° C.

d). In 30 ml. of 50% aqueous acetic acid solution was dissolved 3 g. of 4-benzyloxy-3-nitro - α - (N - benzyl - N - isopropylaminomethyl)benzyl alcohol and after adding to the solution 1.5 g. of iron powder, the mixture was refluxed for 30 minutes under heating. After filtering off insoluble materials from the reaction product, the filtrate was concentrated under a reduced pressure. To the residue thus obtained was added 20 ml. of 5% aqueous sodium carbonate solution and the product was extracted with benzene. The extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated under a reduced pressure to provide brownish crystals of 3 - amino - 4 - benzyloxy - α - (N-benzyl - N - isopropylaminomethyl)benzyl alcohol.

The product, when recrystallized from 2:5 benzene-n-hexane, melted at 63—65° C. The amount of the product obtained was 2.2 g.

e). In 5 ml. of a mixture of acetic anhydride and formic acid was dissolved 1.9 g. of 3-amino-4-benzyloxy-α-(N-benzyl-N-isopropylaminomethyl)benzyl alcohol and after allowing to stand overnight, the solution was concentrated under a reduced pressure. After adding 20 ml. of 5% aqueous sodium carbonate solution to the residue obtained, the product was extracted with 30 ml. of benzene. The extract was washed with water, dried over anhydrous magnesium sulfate, and then concentrated under a reduced pressure to provide benzyl - N - isopropylaminomethyl) - o-4 - benzyloxy - 3 - formylamino - α - (N-formylbenzyl alcohol.

The product was dissolved in 10 ml. of 90% methanol and after adding to the solution 0.5 g. of sodium carbonate, the mixture was stirred for 30 minutes at room temperature. The solvent was distilled off under a reduced pressure and the residue obtained was extracted with benzene. The extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated under a reduced pressure to provide 1.9 g. of brownish oily 4 - benzyloxy - 3 - formylamino - α-(N - benzyl - N - isopropylaminomethyl)-benzyl alcohol.

Reference Preparation 2.

a). In 30 ml. of pyridine was dissolved 5 g. of 3-amino-4-benzyloxyacetophenone and after adding to the solution 3.9 g. of benzyloxyacetyl chloride under cooling, the mixture was stirred overnight at room temperature. The solvent was distilled off from the reaction product under a reduced pressure, the residue formed was dissolved in 50 ml. of chloroform, and then the solution was washed twice with 20 ml. of water. The solution was dried over anhydrous sodium sulfate and chloroform was distilled off under a reduced pressure. By recrystallizing the yellow crystals thus obtained from ethanol, 7.5 g. of 4-benzyloxy - 3 - benzyloxyacetylaminoacetophenone, melting point 104—105° C, was produced.

b). In 50 ml. of chloroform was dissolved 1.9 g. of 4 - benzyloxy - 3 - benzyloxyacetylaminoacetophenone and after adding to the solution 0.78 g. of bromine, the mixture was stirred for 30 minutes at room temperature. Then, chloroform and hydrogen bromide were distilled off from the reaction mixture under a reduced pressure and the crystals obtained were recrystallized from chloroform-n-hexane to provide 1.85 g. of 4-benzyloxy-3-benzyloxyacetylamino - α - bromoacetophenone, melting point 155—157° C.

c). In 100 ml. of tetrahydrofuran was dissolved 4 g. of 4-benzyloxy-3-benzyloxyacetylamino-α-bromoacetophenone at 40—50° C. and after adding to the solution 2.68 g. of N-benzyl-N-isopropylamine, the mixture was stirred overnight at the same temperature as above. The reaction product was cooled, N-benzyl - N - isopropylamine hydrochloride formed was filtered off, then the solvent was distilled off under a reduced pressure. After dissolving the yellow oily material (5 g.) thus obtained in 100 ml. of ethanol, 0.5 g. of sodium borohydride was added to the solution and the mixture was stirred for 4 hours at

room temperature. The solvent was distilled off from the reaction product under a reduced pressure and white crystals obtained were recrystallized from ethanol to give 2.3 g. of 4 - benzyloxy - 3 - benzyloxyacetylamino - α - (N - benzyl - J - isopropylaminomethyl)benzyl alcohol, melting point 93—95° C.

Reference Preparation 3.

a). In 50 ml. of chloroform was dissolved 5.4 g. of 4-hydroxy-3-nitroacetophenone and then 5 ml. of chloroform solution of 4.8 g. of bromine was added dropwise to the solution gradually. Thereafter, the mixture was stirred for 15 minutes and concentrated under a reduced pressure to give yellow crystals. By recrystallizing the product from benzene-n-hexane, 6.3 g. of the crystal of α-bromo-4-hydroxy - 3 - nitroacetophenone melting at 69—71° C. was obtained.

b). In 50 ml. of methyl ethyl ketone was dissolved 5.2 g. of α-bromo-4-hydroxy-3-nitroacetophenone and after adding to the solution 9 g. of N-benzyl-N-isopropylamine, the mixture was stirred overnight at room temperature. After filtering off the hydrobromide of N-benzylisopropylamine thus precipitated, the filtrate was concentrated to provide the crude yellowish brown oily 4-hydroxy-3-nitro-α - (N - benzyl - N - isopropylamino)-acetophenone.

c). In 50 ml. of ethanol was dissolved the crude 4 - hydroxy - 3 - nitro - α - (N-benzyl - N - isopropylamino)acetophenone prepared above and after adding to the solution 1.5 g. of sodium boron hydride, the mixture was stirred overnight at room temperature. The reaction product was concentrated under a reduced pressure and after adding water to the residue obtained, the product was extracted with benzene. The extract was washed with water, dried over anhydrous magnesium sulfate, and then the solvent was distilled off to give a yellow-brown oily material. The oily product was subjected to a silica gel column chromatography using benzene as eluting agent, and from the eluate collected was obtained 4 g. of 4-hydroxy-3-nitro - α - (N - benzyl - N - isopropylaminomethyl)benzyl alcohol.

d). In 30 ml. of methanol was dissolved 2.7 g. of the 4-hydroxy-3-nitro-α-(N-benzyl-N-isopropylaminomethyl)benzyl alcohol prepared above and after adding to the solution 1 g. of Raney nickel catalyst, the catalytic reduction of the compound was conducted at normal temperature and normal pressure. When 600 ml. of hydrogen had been absorbed, the reaction was stopped. After filtering off the catalyst and adding 8.2 ml of 1 normal hydrogen chloride-ethanol solution to the filtrate, the reaction product was concentrated under a reduced pressure to provide 2.7 g. of the yellow-brown powder of 3-amino-4-hydroxy - α - (N - benzyl - N - isopropylaminomethyl)benzyl alcohol hydrochloride.

e). In 20 ml. of pyridine was dissolved 1.2 g. of the 3-amino-4-hydroxy-α-(N-benzyl-N - isopropylaminomethyl)benzyl alcohol hydrochloride prepared above and after adding to the solution 0.20 g. of formic acid and 0.85 g. of dicyclohexylcarbodiimide under cooling below 0° C., the mixture was stirred overnight at room temperature. The dicyclohexyl urea thus precipitated was filtered off, the filtrate was concentrated, and after adding water to the residue, the mixture was washed with ethyl acetate. The aqueous solution formed was neutralized by the addition of sodium carbonate and then extracted with ethyl acetate. The extract was dried and concentrated to give a brown residue. The residue was subjected to a silica gel column chromatography using 5:1 chloroform-acetone mixture as an eluant, and then from the eluate was obtained 0.5 g. of yellow powder of 3-formylamino - 4 - hydroxy - α - (N - benzyl-N-isopropylaminomethyl)benzyl alcohol.

Reference Preparation 4.

a). In 15 ml. of pyridine was dissolved 5 g. of 3 - amino - 4 - benzyloxyacetophenone and after adding to the solution 3 ml. of acetic anhydride, the mixture was allowed to stand for 2 hours at room temperature. The reaction product was then concentrated under a reduced pressure and the crystalline residue obtained was washed with ethanol to provide 5.3 g. of white crystals of 3-acetylamino-4-benzyloxyacetophenone. The product, when reacrystallized from ethanol, melted at 130—133° C.

b). In 45 ml. of chloroform was dissolved 5 g. of 3-acetylamino-4-benzyloxyacetophenone and after adding to the solution dropwise 2.8 g. of bromine in 5 ml. of chloroform gradually while initially warming the system, the mixture was stirred for 20 minutes. 50 ml. of benzene was then added to the mixture and the crystals thus precipitated were recovered by filtration and dried to give 5.5 g. of white crystals of 3-acetylamino-4-benzyloxy - α - bromoacetophenone, melting point 181° C.

c). In 40 ml. of acetonitrile and 10 ml of dimethylformamide was dissolved 1.85 g. of 3 - acetylamino - 4 - benzyloxy - α - bromoacetophenone and after adding to the solution 1.5 g. of N-benzyl-N-isopropylamine followed by stirring for 2 hours at 40—50° C., the mixture was allowed to stand overnight at room temperature. After filtering off the precipitate formed, the filtrate was concentrated under a reduced pressure. The residue was, then, dissolved in ethyl acetate, the insoluble material was filtered off, and ethanol containing dissolved hydrogen chloride gas was added to the filtrate, whereby a crystalline precipitate was formed. The precipitate

was recovered by filtration, dissolved in water with heating, and after filtering off the insoluble material, the solution was neutralized by the addition of aqueous sodium carbonate solution. The reaction product was extracted with ethyl acetate, the extract was, then, washed with water, dried, and concentrated under a reduced pressure to give 1.2 g. of 3 - acetylamino - 4 - benzyloxy - α - (N-benzyl-N-isopropylamino)acetophenone.

d). In 20 ml. of ethanol was dissolved 1 g. of 3 - acetylamino - 4 - benzyloxy - α - (N-benzyl - N - isopropylamino)acetophenone and after adding to the solution 0.2 g. of sodium borohydride, the mixture was stirred overnight. The reaction product was concentrated under a reduced pressure and after adding water to the residue obtained, the product was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated under a reduced pressure to provide 0.9 g. of 3-acetylamino-4-benzyloxy-α-(N-benzyl - N - isopropylaminomethyl)benzyl alcohol.

Reference Preparation 5.

a). In 60 ml. of chloroform was dissolved 5.4 g. of 4-benzyloxy-3-nitroacetophenone and after adding dropwise to the solution a mixture of 3.2 g. of bromine and 5 ml. of chloroform with stirring, the mixture was further stirred for 30 minutes. The reaction product was concentrated under a reduced pressure and the crystalline residue obtained was washed with 20 ml. of benzene and dried to give 5.5 g. of 4-benzyloxy-3-nitro-α-bromoacetophenone melting at 135—136° C.

b). A mixture of 4.6 g. of 4-benzyloxy-3-nitro - α - bromoacetophenone and 6.4 g. of N - benzyl - N - (1 - methyl - 2 - *p*-hydroxyphenylethyl)amine was heated in 50 ml. of methyl ethyl ketone at 70—80° C. for 30 minutes.

After cooling the reaction product, the precipitate formed was filtered off and the filtrate was concentrated under a reduced pressure. When ethanol was added to the residue obtained, the product crystallized. The crystals were recovered by filtration and recrystallized from ethanol to provide, 5.5 g. of 4-benzyloxy-3 - nitro - α [N - benzyl - N - (1 - methyl-2 - *p* - hydroxyphenylethyl)amino] - acetophenone, melting point 84—85° C.

c). In 100 ml. of ethanol was suspended 4.5 g. of 4-benzyloxy-3-nitro-α-[N-benzyl-N - (1 - methyl - 2 - *p* - hydroxyphenylethyl] - amino]acetophenone and after adding to the suspension 0.5 g. of sodium boronhydride, the mixture was stirred for one hour at room temperature. Ethanol was distilled off from the reaction product under a reduced pressure and after adding water to the residue, the product was extracted with benzene. The extract was washed with water, dried over anhydrous magnesium sulfate, and then concentrated under a reduced pressure to give 4.4 g. of yellowish crystalline powder of 4-benzyloxy - 3 - nitro - α - [N - benzyl - N-(1 - methyl - 2 - *p* - hydroxyphenylethyl)-aminoethyl]benzyl alcohol.

d). In 40 ml. of 60% aqueous acetic acid solution was dissolved 4.3 g. of 4-benzyloxy-3 - nitro - α - [N - benzyl - N - (1 - methyl-2 - *p* - hydroxyphenylethyl)aminomethyl]-benzyl alcohol and after adding to the solution 1.5 g. of iron powder, the mixture was refluxed for 30 minutes. After filtering off insoluble material from the reaction product, the filtrate was concentrated under a reduced pressure. To the residue obtained was added 10% aqueous sodium carbonate solution and the product was extracted with benzene. The extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated under a reduced pressure to give 3.7 g. of brownish crystalline powder of 3-amino-4 - benzyloxy - α - [N - benzyl - N - (1-methyl - 2 - *p* - hydroxyphenylethyl)aminomethyl]benzyl alcohol.

e). In 10 ml. of 5:3 acetic anhydride-formic acid mixture was dissolved 3.3 g. of 3 - amino - 4 - benzyloxy - α - [N - benzyl-N - (1 - methyl - 2 - *p* - hydroxyphenylethyl)aminomethyl]benzyl alcohol and after standing overnight at room temperature, the mixture was concentrated under a reduced pressure. The residue obtained was dissolved in 50 ml. of methanol and after adding to the solution 3 ml. of water and 3 g. of sodium carbonate, the mixture was stirred for one hour at room temperature. Methanol was distilled off under a reduced pressure and the residue was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate, and the solvent was distilled off to give 3.4 g. of faint-brown powder of 4-benzyloxy-3-formylamino-α - [N - benzyl - N - (1 - methyl - 2 - *p*-hydroxyphenylethyl)aminomethyl]benzyl alcohol. In 30 ml. of benzene was dissolved 2.5 g. of the faint brown powder obtained above and the solution was allowed to stand overnight at room temperature, whereby crystals were formed. The crystals were separated and recrystallized from ethyl acetatebenzene to give 1.2 g. of white crystals, melting point 135—137° C.

Nuclear magnetic resonance spectrum: ($CDCl_3$),

δ:4.50 ppm. (m, 1H, cH at the root of hydroxyl group), 3.46, 3.87 ppm. (AB pattern, q, 2H, cH_2 at the root of N).

This product is called 4-benzyloxy-3-formylamino - α - {N - benzyl - N - (1-methyl - 2 - *p* - hydroxyphenylethyl)aminomethyl]benzyl alcohol [A].

The solvent was distilled off from the mother liquor left from the final step above and the residue thus obtained was subjected

to a silica gel column chromatography. By using 10:2 benzene ethyl acetate mixture as eluent, 0.8 g. of a white crystalline powder was obtained.

Nuclear magnetic resonance spectrum: ($CDCl_3$)

δ:4.34 ppm (m, 1H, cH at the root of hydroxyl group), 3.76 ppm. (S, 2H, cH_2 at the root of N).

This product is 4-benzyloxy-3-formylamino - α - [N - benzyl - N - (1 - methyl-2 - *p* - hydroxyphenylethyl)aminomethyl]-benzyl alcohol [B].

Reference Preparation 6.

a). In 270 ml. of chloroform was dissolved 27 g. of 4-benzyloxy-3-nitroacetophenone and after adding dropwise to the solution a mixture of 16 g. of bromine and 10 ml. of chloroform gradually with stirring, the mixture was further stirred for 30 minutes. The reaction mixture was concentrated under a reduced pressure and the crystalline residue obtained was washed with a mixture of 50 ml. of benzene and 50 ml. of n-hexane and dried to give 31 g. of 4-benzyloxy-3-nitro-α-bromoacetophenone, melting point 135—136° C.

b). A mixture of 30.5 g of 4-benzyloxy-3-nitro-α-bromoacetophenone and 28.5 g. of N-benzyl-N-*t*-butylamine was refluxed together with 300 ml. of methyl ethyl ketone for 3 hours. After cooling, the precipitate thus formed was filtered off. The filtrate was concentrated under a reduced pressure and the crystals formed were recovered and recrystallized from ethanol to give 30 g. of 4-benzyloxy-3-nitro-α - (N - benzyl - N - *t* - butylamino)-acetophenone, melting point 99—100° C.

c). In a mixture of 200 ml. of ethanol and 150 ml. of tetrahydrofuran was dissolved 30 g. of 4-benzyloxy-3-nitro-α-(N-benzyl-N-*t*-butylamino)acetophenone and after adding to the solution 3 g. of sodium borohydride, the mixture was stirred for 3 hours at room temperature. The reaction product was concentrated under a reduced pressure and after adding water to the residue, the product was extracted with benzene. The extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated under a reduced pressure to give 30 g. of oily 4-benzyloxy - 3 - nitro - α - (N - benzyl - N-*t*-butylaminomethyl)benzyl alcohol.

d). In 150 ml. of 50% aqueous acetic acid solution was dissolved 30 g. of 4-benzyloxy - 3 - nitro - α - (N - benzyl - N - *t*-butylaminomethyl)benzyl alcohol and after adding to the solution 12 g. of iron powder, the mixture was refluxed for 25 minutes. While the reaction mixture was in a hot state, it was filtered and the filtrate was concentrated under a reduced pressure. Then, after adding to the residue 50 ml. of 10% aqueous sodium carbonate solution, the product was extracted with benzene. The extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated under a reduced pressure to give a crystalline residue. By recrystallizing the product from a mixture of 40 ml. of benzene and 60 ml. of n-hexane, 23 g. of 3-amino-4-benzyloxy-α-(N - benzyl - N - *t* - butylaminomethyl)-benzyl alcohol, melting point 68—69° C., was obtained.

e). In 50 ml. of 5:3 acetic anhydride-formic acid was dissolved 20 g. of 3-amino-4-benzyloxy - α - (N - benzyl - N - *t* - butylaminomethyl)benzyl alcohol and after allowing to stand overnight, the solution was concentrated under a reduced pressure. The residue obtained was dissolved in 120 ml. of methanol and after adding to the solution 5 ml. of water and 7.5 g. of sodium carbonate, the mixture was stirred for one hour at room temperature. The solvent was distilled off from the reaction mixture under a reduced pressure and the residue obtained was extracted with benzene. The extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated under a reduced pressure to give 2005 g. of oily 4-benzyloxy-3 - formylamino - α - (N - benzyl - N - *t*-butylaminomethyl)benzyl alcohol.

f). In 30 ml. of anhydrous tetrahydrofuran was dissolved 5 g. of 4 - benzyloxy - 3-formylamino - α - (N - benzyl - N - *t*-butylaminomethyl)benzyl alcohol and the resultant solution was added dropwise with stirring to a solution of 20 ml. of tetrahydrofuran and 20 ml. of ether having added thereto 3 g. of lithium hydride. Thereafter, the resultant mixture was refluxed for one hour. After adding 20 ml. of water dropwise to the reaction mixture followed by stirring for one hour, the reaction mixture was filtered and the filtrate was concentrated under a reduced pressure. The residue was extracted with benzene and the extract was washed with water, dried, and concentrated under a reduced pressure. The residue was subjected to a silica gel (70 ml.) column chromatography, the 3rd—8th fractions (each fraction 40 ml.) collected using chloroform as eluant were concentrated under a reduced pressure to provide 2.8 g. of faint-yellow oily 4-benzyloxy - 3 - methylamino - α - (N-benzyl - N - *t* - butylaminomethyl)benzyl alcohol.

g). In 5 ml. of 5:3 acetic anhydride-formic acid mixture was dissolved 1.5 g. of 4 - benzyloxy - 3 - methylamino - α - (N-benzyl - N - *t* - butylaminomethyl)benzyl alcohol and the solution was allowed to stand overnight. The mixture was, then, concentrated under a reduced pressure, the residue obtained was dissolved in 50 ml. of methanol, and after adding to the solution 3 ml. of chilled water and 2 g. of sodium carbonate, the resultant mixture was stirred for one hour.

The reaction product was concentrated under a reduced pressure and the residue obtained was extracted with benzene. After washing the extract with water followed by drying over magnesium sulfate, the solvent was distilled off under a reduced pressure to give 1.5 g. of brownish oily 4-benzyloxy-3-(N-methyl-N - formylamino) - α - (N - benzyl - N - *t*-butylaminomethyl)benzyl alcohol.

Reference Preparation 7.

a). In 100 ml. of chloroform was dissolved 16.5 g. of *p*-nitroacetophenone and after adding dropwise to the solution 16 g. of bromine at room temperature, the mixture was stirred for 30 minutes. When the solvent was distilled off from the mixture under a reduced pressure, yellow crystals were obtained. By recrystallizing the crystals from benzene-n-hexane, 18.8 g.of 4-nitro-α-bromoacetophenone, melting point 100—101° C., was obtained. The yield was 77%.

Elemental analysis for $C_8H_6NO_3Br$:

	C(%)	H(%)	N(%)	Br(%)
Calculated:	39.37	2.48	5.74	32.74
Found:	39.22	2.30	5.41	32.33

b). In 50 ml. of anhydrous acetonitrile was dissolved 10 g. of α-bromo-4-nitroacetophenone and after adding to the solution 13.7 g. of N-benzyl-N-tert-butylamine at normal temperature, the mixture was stirred for 2 hours. After distilling off the solvent under a reduced pressure, 100 ml. of benzene was added to the residue and after filtering off the hydrobromide of N-benzyl-N-tert-butylamine formed, benzene was distilled off under a reduced pressure to give a red-black liquid. When 10 ml. of ethanol was added to the liquid, crystals were formed, which were recovered by filtration and recrystallized from ethanol to provide 3.5 g. of yellow acicular crystals of 4-nitro-α-(N-benzyl-N-*t*-butylamino)acetophenone, melting point 88—90°C.

Elementary analysis for $C_{19}H_{22}N_2O_3$:

C	C(%)	H(%)	N(%)
Calculated:	69.92	6.79	8.58
Found:	69.73	6.81	8.71

c). In 200 ml. of ethanol was dispersed 5 g. of 4-nitro-α-(N-benzyl-N-*t*-butylamino)-acetophenone and after adding to the dispersion 1 g. of sodium boronhydride, the mixture was stirred at room temperature, whereby the acetophenone dissolved gradually. When the compound dissolved completely, the solution was stirred for 30 minutes and then the solvent was distilled off under a reduced pressure to give yellow crystals. By recrystallizing the crystals from ethanol, 4 g. of yellow acicular crystals of 4-nitro-α-(N-benzyl-N-*t*-butylaminomethyl)benzyl alcohol, melting point 111—112° C were obtained.

Elemental analysis for $C_{19}H_{24}N_2O_3$:

	C(%)	H(%)	N(%)
Calculated:	69.49	7.37	8.53
Found:	69.19	7.49	8.72

d). In 100 ml. of anhydrous methanol was dissolved 4 g. of 4-nitro-α-(N-benzyl-N-*t*-butylaminomethyl)benzyl alcohol and after adding to the solution 1 g. of Raney nickel, the catalytic reduction was conducted at normal temperature and pressure until 1080 ml. of hydrogen had been absorbed. After filtering off the catalyst, the solvent was distilled off under a reduced pressure to provide an oily residue. By purifying the oily residue by chromatography using a 100 ml. silica gel column and using benzene as a developing solvent, a yellow liquid was obtained. When the liquid was allowed to stand at room temperature, crystals formed, which were recovered by filtration and recrystallized from ethanol-n-hexane to provide 2.13 g. of yellow acicular crystals of 4-amino-α-(N-benzyl-N-*t*-butylaminoethyl)benzyl alcohol, melting point 88—90° C.

Elemental analysis for $C_{19}H_{26}N_2O$:

	C(%)	H(%)	N(%)
Calculated	76.47	8.78	9.39
Found:	76.59	9.11	9.53

e). In 10.6 ml. of 5:3 acetic anhydride-formic acid mixture was dissolved 2.13 g. of 4 - amino - α - (N - benzyl - N - *t* - butylaminomethyl)benzyl alcohol and the solution was stirred overnight at room temperature. When the excessive acetic anhydride and formic acid were distilled off under a reduced pressure, an oily material was obtained. The oily product was dissolved in 30 ml. of methanol and after adding to the solution 5 ml. of water and an excess amount of sodium carbonate, the resultant mixture was stirred for one hour at room temperature. The solvent was, then, distilled off from the reaction mixture under a reduced pressure. The oily material thus obtained was dissolved in 50 ml. of benzene, and the solution was washed with water until the washing became neutral. After drying the solution over anhydrous magnesium sulfate, the solvent was distilled off under a reduced pressure to give 2 g. of caramel-like 4-formylamino-α-(N-benzyl - N - *t* - butylaminomethyl)benzyl alcohol.

The nuclear magnetic resonance spectra and infrared absorption spectra of the product coincided with those of the proposed structure.

Reference Preparation 8.

a).

In 200 ml. of methanol was dissolved 16.0 g. of the 4-benzyloxy-3-formylamino-α-[N-benzyl - N - (1 - methyl - 2 - *p* - hydroxy-

phenylethyl)aminomethyl]benzyl alcohol [A] prepared in Reference Preparation 5 and after adding to the solution 30 ml. of 4.8 normal hydrochloric acid, the mixture was refluxed for one hour and 30 minutes. On completion of the reaction, the product was cooled and after adding thereto 10 g. of potassium hydroxide and 50 ml. of water, the resultant mixture was stirred for one hour. The solvent was distilled off from the reaction product under a reduced pressure and the residue obtained was extracted with benzene. The extract was washed with water, dried over anhydrous magnesium sulfate, and then concentrated under a reduced pressure to provide 14.5 g. of crystalline powder of 3-amino-4 - benzyloxy - α - [N - benzyl - N - (1-methyl - 2 - *p* - hydroxyphenylethyl)aminomethyl]benzyl alcohol [A].

b).

In 20 ml. of acetic anhydride was dissolved 4.0 g of 3-amino-4-benzyloxy-α-[N-benzyl-N - (1 - methyl - 2 - *p* - hydroxyphenylethyl)aminomethyl]benzyl alcohol [A] prepared above and after heating the mixture to 65—80° C for one hour and 30 minutes, the reaction mixture was concentrated under a reduced pressure. The residue was dissolved in a mixture of 15 ml. of methanol and 2.0 g. of potassium hydroxide and the solution was stirred for one hour at room temperature. Methanol was then distilled off under a reduced pressure and after addition of water to the residue, the residue was extracted with benzene. The extract was washed with water, dried over anhydrous magnesium sulfate, and dried. Thereafter, by distilling off the solvent, 3.8 g. of crystalline powder of 4-benzyloxy-3-acetylamino - α - [N - benzyl - N - (1-methyl - 2 - *p* - hydroxyphenylethyl)aminomethyl]benzyl alcohol [A] was obtained. By recrystallizing 2.0 g. of the product thus obtained from 20 ml. of ethanol 1.6 g. of pure crystalline product was obtained, melting point 141—143° C.

Elemental analysis for $C_{38}H_{36}N_2O_4$:

	C(%)	H(%)	N(%)
Calculated	75.55	6.92	5.34
Found:	75.62	7.03	5.21

Reference Preparation 9.

In 20 ml. of anhydrous pyridine was dissolved 2 g. of the 3-amino-4-benzyloxy-α-[N - benzyl - N - (1 - methyl - 2 - *p*-hydroxyphenylethyl)aminomethyl]benzyl alcohol prepared in the aforesaid Reference Preparation 8-a) and the solution was cooled to a temperature of from −20 to −30° C. A solution of 2.28 g. of benzyloxyacetyl chloride in 5 ml. of toluene was added dropwise to the solution thus cooled and while stirring the mixture, the temperature of the mixture was elevated slowly to room temperature. After stirring the mixture overnight, the solvent was distilled off under a reduced pressure and the residue was mixed with 50 ml. of benzene and 50 ml. of water. After washing the benzene solution thus obtained thrice with water, benzene was distilled off under reduced pressure to provide a red oily material. This product was dissolved in 50 ml. of ethanol and after adding to the solution 5 ml. of water and 10 ml. of 4 normal sodium hydroxide solution, the resultant mixture was stirred for two hours. After adjusting the pH of the reaction mixture to 3 by adding 1 normal hydrochloric acid, an excess amount of sodium carbonate was added thereto. Ethanol was distilled off under a reduced pressure and the residue was extracted with benzene. The extract was washed thrice with water, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure to provide a yellow oily material. This product was, then, subjected to a silica gel column chromatography (65 ml.) using 9:1 benzene-acetone mixture as eluant and the eluate was concentrated under reduced pressure to provide 3-benzyloxyacetylamino-4-benzyloxy - α - [N - benzyl - N - (1 - methyl-2 - *p* - hydroxyphenylethyl)aminomethyl]-benzyl alcohol.

Nuclear magnetic resonance spectrum ($CDCl_3$):

δ: 1.00 ppm. (d, 3H, CH—CH_3), 4.08 ppm.

$$\overset{O}{\overset{\|}{C}}H_2O-)$$

(S, 2H, —C

The invention will further be explained practically by the following Examples.

Example 1.

In 20 ml. of ethanol was dissolved 1.4 g. of 4 - benzyloxy - 3 - formylamino - α - (N-benzyl - N - isopropylaminoethyl)benzyl alcohol and after adding to the solution 0.2 g. of 10% palladium on carbon, the catalytic reduction was carried out at normal temperature and pressure. After 165 ml. of hydrogen had been absorbed, the reaction was stopped. The catalyst was filtered off, the solvent was distilled off under a reduced pressure, and then the residue obtained was dissolved in a small amount of ethanol. Thereafter, when a small amount of ether was added to the solution and the solution was allowed to stand, crystals were precipitated. By recovering the crystals by filtration, 0.7 g. of 3-formylamino-4-hydroxy - α - (isopropylaminomethyl)benzyl alcohol was obtained.

When 120 mg. of the product obtained above was added to 2 ml. of ethanol solution containing 30 mg. of fumaric acid and the mixture allowed to stand, white crystals were precipitated. The crystals were recovered by filtration to provide 3-formylamino-4-

hydroxy - α - (isopropylaminomethyl)benzyl alcohol ½ fumarate melting point 179—190° C. (decomposed).

Elemental analysis for $C_{14}H_{20}N_2O_5$:

	C(%)	H(%)	N(%)
Calculated:	56.75	6.80	9.45
Found:	56.71	6.76	9.70

Example 2.

In 100 ml. of methanol was dissolved 2.3 g. of 4 - benzyloxy - 3 - benzyloxyacetylamino-α - (N - benzyl - N - isopropylaminomethyl)-benzyl alcohol and after adding to the solution 4.3 ml. of a 1N solution of hydrogen chloride in ethanol and then 0.3 g. of 10% palladium on carbon, the catalytic reduction was conducted at normal temperature and pressure. When 300 ml. of hydrogen had been absorbed, the reaction was stopped. Thereafter, the catalyst was filtered off and then the solvent was distilled off under a reduced pressure to provide white crystals. By crystallizing the crystals from methanol-n-hexane, 600 mg. of 4-hydroxy-3-hydroxyacetylamino-α - (isopropylaminomethyl)benzyl alcohol hydrochloride, melting point 188—190° C. was obtained.

Elemental analysis for $C_{13}H_{20}N_2O_4.HCl$:

	C(%)	H(%)	N(%)
Calculated:	51.23	6.95	9.19
Found:	50.79	7.03	9.03.

Example 3.

In 20 ml. of ethanol was dissolved 1 g. of 3 - acetylamino - 4 - benzyloxy - α - (N-benzyl - N - isopropylaminomethyl)benzyl alcohol and after adding to the solution 0.2 g. of 10% palladium on carbon, the catalytic reduction was conducted at normal temperature and pressure. When 115 ml. of hydrogen had been absorbed, the reaction was stopped. The catalyst was filtered off and the reaction product was concentrated under a reduced pressure to give an oily material. The oily material was dissolved in ethyl acetate and then a 3 N ethanol solution of hydrogen chloride was added, whereby crystals formed. The solvent was removed by decantation and the crystals were washed with ethyl acetate and dried to give 0.5 g. of crystalline powder of 3 - acetylamino - 4 - hydroxy - α - (isopropylaminomethyl)benzyl alcohol hydrochloride.

Elemental analysis for $C_{13}H_{20}N_2O_3.HCl$:

	C(%)	H(%)	N(%)
Calculated:	54.07	7.33	9.70
Found:	53.81	7.28	9.63

Example 4.

In 20 ml. of ethyl acetate was dissolved 1.4 g. of 4 - benzyloxy - 3 - ethoxycarbonylamino - α - (N - benzyl - N - isopropylaminomethyl)benzyl alcohol and after adding to the solution 0.2 g. of 10% palladium on carbon, the catalytic reduction was conducted at normal temperature and pressure. When 145 ml. of hydrogen had been absorbed, the reaction was stopped. The catalyst was filtered off and the reaction product was concentrated under a reduced pressure to give an oily material. The oily material was dissolved in 2 ml. of ether and 30 ml. of a 3N solution of hydrogen chloride in ethanol was added to the solution, whereby crystals formed. The crystals were recovered by filtration and recrystallized from 1:1 ethanol-ether to give 0.6 g. of 3-ethoxycarbonylamino-4-hydroxy-α - (isopropylaminomethyl)benzyl alcohol hydrochloride, melting point 178° C.

Elemental analysis for $C_{14}H_{22}N_2O_4.HCl$:

	C(%)	H(%)	N(%)
Calculated:	52.75	7.27	8.79
Found:	52.75	7.32	8.81

Example 5.

In 30 ml. of ethanol was dissolved 2.5 g. of 4 - benzyloxy - 3 - formylamino - α - (N-benzyl - N - *t* - butylaminomethyl)benzyl alcohol and after adding to the solution 0.2 g. of 10% palladium on carbon, the catalytic reaction was conducted at normal temperature and pressure. When 280 ml. of hydrogen had been absorbed, the reaction was stopped. After filtering off the catalyst, the reaction product was concentrated under a reduced pressure to give 1.3 g. of the crystalline powder of 3-formylamino - 4 - hydroxy - α - (tert - butylaminomethyl)benzyl alcohol. When 1.2 g. of this product was added to 15 ml. of ethanol having dissolved therein 0.3 g. of fumaric acid and the mixture was allowed to stand overnight at −4° C., white crystals formed. By recovering the crystals by filtration, 1.14 g. were obtained of 3-formylamino-4-hydroxy-α - (*t* - butylaminomethyl)benzyl alcohol. ½ fumarate, melting point 195—196° C.

Elemental analysis for $C_{15}H_{22}N_2O_5$:

	C(%)	H(%)	N(%)
Calculated:	58.05	7.15	9.03
Found:	58.03	7.21	8.94

Example 6.

In 15 ml. of ethanol was dissolved 1 g. of 3 - acetylamino - 4 - benzyloxy - α - (N-benzyl - N - isopropylamino)acetophenone and after adding to the solution 0.2 g. of 10% palladium on carbon, the catalytic reduction was conducted under normal temperature and pressure. When 168 ml. of hydrogen had been absorbed, the reaction was stopped. After filtering off the catalyst, the reaction product was concentrated under reduced pressure to give 0.45 g. of crude 3-acetylamino-4-hydroxy - α - (isopropylaminomethyl)benzyl alcohol. When 250 mg. of the product was

added to 5 ml. of ethanol solution of 60 mg. of fumaric acid and the mixture was allowed to stand, crystals were formed, which were recovered by filtration to provide 150 mg. of 3 - acetylamino - 4 - hydroxy - α - (isopropylaminomethyl)benzyl alcohol ½ fumarate melting at 189—192° C.

Elemental analysis for $C_{15}H_{22}N_2O_5$:

	C(%)	H(%)	N(%)
Calculated:	58.05	7.15	9.03
Found:	57.72	7.26	8.93

Example 7.

In 10 ml. of methanol was dissolved 0.7 g. of 4 - benzyloxy - 3 - formylamino - α - (N-isopropyl-N-benzylamino)acetophenone and after adding to the solution 0.2 g. of 10% palladium on carbon, the catalytic reduction was carried out at normal temperature and pressure. When 120 ml. of hydrogen had been absorbed, the reaction was stopped. After filtering off the catalyst, the reaction product was concentrated to give 0.3 g. of crude 3-formylamino-4 - hydroxy - α - (N - isopropylaminomethyl)benzyl alcohol. 240 mg. of this product was dissolved in 3 ml. of ethanol and after adding to the solution 60 mg. of fumaric acid, the mixture was allowed to stand at room temperature to form crystals which were recovered by filtration to provide 75 mg. of 3 - formylamino - 4 - hydroxy - α - (isopropylaminomethyl)benzyl alcohol ½ fumarate, melting point 179—181° C.

The product showed the same infrared absorption spectra as the product obtained in Example 1.

Example 8.

In 20 ml. of ethanol was dissolved 1 g. of 4 - benzyloxy - 3 - formylamino - α - (N-benzyl - N - *t* - butylamino)acetophenone and after adding to the solution 0.2 g. of 10% palladium on carbon, the catalytic reduction was conducted at normal temperature and pressure. When 165 ml. of hydrogen had been absorbed, the reaction was stopped. After filtering off the catalyst, the reaction product was concentrated to give 0.5 g. of crude 3 - formylamino - 4 - hydroxy - α-(*t*-butylaminomethyl)benzyl alcohol. When 250 mg. of the product was added to 5 ml. ethanol solution having dissolved therein 60 mg. of fumaric acid and then the mixture allowed to stand at room temperature, crystals formed, which were recovered by filtration to provide 100 mg. of 3-formylamino-4-hydroxy - α - (*t* - butylaminomethyl)benzyl alcohol. ½ fumarate, melting point 195—196° C.

The product showed the same infrared absorption spectra as the compound prepared in Example 5.

Example 9.

In 10 ml. of ethanol was dissolved 0.45 g. of 3 - formylamino - 4 - hydroxy - α - (N-benzyl - N - isopropylaminomethyl)benzyl alcohol and after adding to the solution 0.1 g. of 10% palladium on carbon, the catalytic reduction was carried out at normal temperature and pressure. When 36 ml. of hydrogen had been absorbed, the reaction was stopped. After filtering off the catalyst, the reaction product was concentrated under a reduced pressure to give 0.32 g. of the white crystalline powder of 3-formylamino-4-hydroxy-α-(isopropylaminomethyl)benzyl alcohol. 240 mg. of this product was dissolved in 3 ml. of ethanol and after adding thereto 60 mg. of fumaric acid, the mixture was allowed to stand at room temperature, 250 mg. of white crystals of 3 - formylamino - 4 - hydroxy - α - (isopropylaminomethyl)benzyl alcohol. ½ fumarate was obtained.

The product showed the same infrared absorption spectra as the product obtained in Example 1.

Example 10.

In 10 ml. of ethanol was dissolved 0.9 g. of 3 - formylamino - 4 - hydroxy - α - (N-benzyl - N - *t* - butylaminomethyl)benzyl alcohol and after adding to the solution 0.1 g. of 10% palladium on carbon, the catalytic reduction was carried out at normal temperature and pressure. When 65 ml. of hydrogen had been absorbed, the reaction was stopped. After filtering off the catalyst, the reaction product was concentrated under a reduced pressure to give 0.65 g. of white crystalline powder of 3 - formylamino - 4 - hydroxy-α - (*t* - butylaminomethyl)benzyl alcohol. 500 mg. of the product was dissolved in 5 ml. of ethanol and after adding to the solution 120 mg. of fumaric acid, the mixture was allowed to stand at room temperature, when crystals formed. The crystals were recovered by filtration to provide 520 mg. of 3-formylamino - 4 - hydroxy - α - (*t* - butylaminomethyl)benzyl alcohol. ½ fumarate.

The product showed the same infrared absorption spectra as the aimed product prepared in Example 5.

Example 11.

In 20 ml. of ethanol was suspended 1.1 g. of the 4 - benzyloxy - 3 - formylamino - α-[N - benzyl - N - (1 - methyl - 2 - *p*-hydroxyphenylethyl)aminomethyl]benzyl alcohol [A] prepared in Reference Preparation 5 and after adding to the suspension 0.1 g. of 10% palladium on carbon, the catalytic reduction was conducted at normal temperature and pressure until 105 ml. of hydrogen had been absorbed. After filtering off the catalyst, the reaction product was concentrated under a reduced pressure to give 0.7 g. of white crystalline powder of 3-formylamino-4 - hydroxy - α - [N - (1 - methyl - 2-p - hydroxyphenylethyl)aminomethyl]benzyl alcohol [A].

When 0.34 g. of the product prepared above was dissolved in 95% ethanol together with 0.06 g. of fumaric acid and the solution was allowed to stand, crystals formed, which were recovered to provide 0.33 g. of 3 - formylamino - 4 - hydroxy - α - [N-(1 - methyl - 2 - p - hydroxyphenylethyl)-aminomethyl]benzyl alcohol [A]. $\frac{1}{2}$ fumarate, melting point 151.8—153° C.

Elemental analysis for $C_{20}H_{24}N_2O_6$:

	C(%)	H(%)	N(%)
Calculated:	61.85	6.23	7.21
Found:	61.52	6.31	7.31

Example 12.

In 10 ml. of ethanol was dissolved 1.0 g. of the 4 - benzyloxy - 3 - formylamino - α-[N - benzyl - N - (1 - methyl - 2 - p-hydroxyphenylethyl)aminomethyl]benzyl alcohol [B] prepared in Reference Preparation 5 and after adding to the solution 0.1 g. of 10% palladium on carbon, the catalytic reduction was conducted at normal temperature and pressure until 95 ml. of hydrogen had been absorbed. After filtering off the catalyst, the reaction product was concentrated under a reduced pressure to give 0.65 g. of faint-brownish powder of 3 - formylamino-4 - hydroxy - α - [N - (1 - methyl - 2 - p-hydroxyphenylethyl)aminomethyl]benzyl alcohol [B].

When 0.34 g. of the product prepared above was dissolved in 95% ethanol together with 0.06 g of fumaric acid and the solution was allowed to stand, crystals formed, which were recovered to provide 0.3 g of 3-formylamino-4 - hydroxy - α - [N - (1 - methyl - 2 - p-hydroxyphenylethyl)aminomethyl]benzyl alcohol [B] $\frac{1}{2}$ fumarate, melting point 154.1—155° C.

Elemental analysis for $C_{20}H_{24}N_2O_6$:

	C(%)	H(%)	N(%)
Calculated:	61.85	6.23	7.21
Found:	61.73	6.27	7.19

Example 13.

In 20 ml. of ethanol was dissolved 1.5 g. of 4 - benzyloxy - 3 - formylamino - α - N-benzyl - N - (1 - methyl - 3 - cyclohexylpropyl)aminomethyl]benzyl alcohol and after adding to the solution 0.2 g. of 10% palladium on carbon, the catalytic reduction was conducted at normal temperature and pressure until 140 ml. of hydrogen had been absorbed. After filtering off the catalyst, the reaction product was concentrated under a reduced pressure to provide 0.9 g. of white crystalline powder of 3 - formylamino - 4 - hydroxy - α-[N - (1 - methyl - 3 - cyclohexylpropyl)-aminomethyl]benzyl alcohol.

470 mg. of the product was dissolved in 7 ml. of 0.2N solution of acetic acid in ethanol, the solution was concentrated to 2—3 ml., and after adding ether thereto, the mixture was allowed to stand, when white crystals formed. The crystals were recovered by filtration to provide 0.5 g. of 3-formylamino-4-hydroxy - α - [N - (1 - methyl - 3 - cyclohexylpropyl)aminomethyl]benzyl alcohol acetate, melting point 138—140° C.

Elemental analysis for $C_{21}H_{34}N_2O_5$:

	C(%)	H(%)	N(%)
Calculated:	63.94	8.69	7.10
Found:	64.31	8.92	7.46

Example 14.

In 30 ml. of ethanol was dissolved 2.7 g. of the 4 - benzyloxy - 3 - methylamino - α-(N - benzyl - N - t - butylaminomethyl)-benzyl alcohol prepared in Reference Preparation 6-f) and after adding to the solution 0.3g. of 10% palladium on carbon, the catalytic reduction was carried out at normal temperature and pressure until 310 ml. of hydrogen had been absorbed. After filtering off the catalyst, the reaction product was concentrated under a reduced pressure to provide 1.3 g. of powder of 4-hydroxy-3-methylamino-α-(t-butylaminomethyl)benzyl alcohol. When ethanol was added to the product, white crystals formed. The product, when recrystallized from ethanol, melted at 173° C.

Elemental analysis for $C_{13}H_{22}N_2O_2$:

	C(%)	H(%)	N(%)
Calculated:	65.52	9.30	11.75
Found:	65.43	9.57	11.52

Example 15.

In 20 ml. of ethanol was dissolved 1.4 g. of the 4-benzyloxy-3-(N-methyl-N-formylamino) - α - (N - benzyl - N - t - butylaminomethyl)benzyl alcohol (prepared in Reference Preparation 6-g) and after adding to the solution 0.1 g. of 10% palladium on carbon, the catalytic reduction was conducted until 150 ml. of hydrogen had been absorbed. After filtering off the catalyst, the reaction product was concentrated under a reduced pressure to provide 0.8 g. of white crystalline powder of 4-hydroxy-3-(N-methyl-N-formylamino)-α-(t-butylaminomethyl)benzyl alcohol. 360 mg. of the product was dissolved in 6 ml. of ethanol together with 85 mg. of fumaric acid and the solution was allowed to stand, when white crystals formed. The crystals were recovered by filtration to provide 390 mg. of 4 - hydroxy - 3 - (N - methyl - N - formylamino) - α - (t - butylaminomethyl)benzyl alcohol $\frac{1}{2}$ fumarate melting point 188° C.

Elemental analysis for $C_{16}H_{24}N_2O_5$:

	C(%)	H(%)	N(%)
Calculated:	59.24	7.46	8.64
Found:	59.16	7.47	8.34

Example 16.

In 100 ml. of anhydrous methanol was dissolved 1.8 g. of 4-formylamino-α-(N-benzyl-N - *t* - butylaminomethyl)benzyl alcohol and after adding to the solution 100 mg. of 10% palladium on carbon, the catalytic reduction was conducted at normal temperature and pressure until the absorption of hydrogen stopped completely. After filtering off the catalyst, the solvent was distilled off under reduced pressure to provide 1.46 g. of a caramel-like material. The product was dissolved in 20 ml. of ethanol and after adding to the solution 358 mg. of fumaric acid, the mixture was allowed to stand at 4° C., whereby white acicular crystals precipitated, which were recovered by filtration to give 950 mg. of 4-formylamino - α - (N - *t* - butylaminomethyl)-benzyl alcohol. ½ fumarate, melting point 125—127° C.

Elemental analysis for $C_{25}H_{22}N_2O_4$:

	C(%)	H(%)	N(%)
Calculated:	61.21	7.53	9.52
Found:	60.93	7.70	9.23

Example 17.

In 15 ml. of ethanol was dissolved 1.1 g. of 3 - formylamino - α - (N - benzyl - N-*t* - butylaminomethyl)benzyl alcohol and after adding to the solution 0.1 g. of 10% palladium on carbon, the catalytic reduction was conducted at normal temperature and pressure until 76 ml. of hydrogen had been absorbed. After filtering off the catalyst, the reaction product was concentrated under a reduced pressure to give 750 mg. of a white crystalline powder.

470 mg. of the product prepared above and 116 mg. of fumaric acid were dissolved in 3 ml. of ethanol and after adding ether to the solution until it became turbid slightly, the mixture was allowed to stand, whereby white crystals formed, which were recovered by filtration to provide 530 mg. of 3-formylamino - α - (N - *t* - butylaminomethyl)benzyl alcohol. ½ fumarate melting point 182° C.

Elemental analysis for $C_{25}H_{22}N_2O_4$:

	C(%)	H(%)	N(%)
Calculated:	61.21	7.53	9.52
Found:	61.16	7.76	9.44

Reference Preparation 10.

In 30 ml. of anhydrous pyridine were dissolved 4 g. of 3-amino-4-benzyloxy-α-[N-benzyl - N - (1 - methyl - 2 - *p*-hydroxyphenylethyl)aminomethyl]benzyl alcohol hydrochloride and 3.5 g. of N-acetyl-β-alanine and after adding 5.5 g of dicyclohexylcarbodiimide to the solution under ice-cooling, the mixture was stirred overnight. After filtering off the precipitate thus formed, the reaction mixture was concentrated under a reduced pressure and the residue was dissolved in 30 ml. of methanol. After adding 10 ml. of 4 normal sodium hydroxide solution, the mixture was stirred for 3 hours followed by adding thereto 1′ normal hydrochloric acid solution to adjust the pH to 3 and then adding excess sodium carbonate, after which the resultant mixture was stirred for 30 minutes. The reaction product was concentrated under a reduced pressure and then extracted with 50 ml. of chloroform. The extract was washed thrice with water, dried over anhydrous magnesium sulfate, and concentrated under a reduced pressure to give 4 g. of a yellow oily material. By subjecting the product to a silica gel column chromatography (75 ml.) and then to a silica gel column chromatography (35 ml.), 800 mg. of pure caramel-like 3 - (N - acetyl - β-alanyl)amino - 4 - benzyloxy - α - [N-benzyl - N - (1 - methyl - 2 - *p* - hydroxyphenylethyl)aminomethyl]benzyl alcohol was obtained. In the above chromatographic purification treatments, 4:2:1 ethyl acetate-benzene-methanol was used as the development solvent.

Elemental analysis for $C_{36}H_{41}N_3O_5$:

	C(%)	H(%)	N(%)
Calculated:	72.58	6.94	7.05
Found:	72.44	6.98	6.86

Reference Preparation 11.

a). A mixture of 4.1 g. of 4-benzyloxy-3-nitro-α-bromoacetophenone, 6.6 g. of N-benzyl - N - (1 - methyl - 2 - *p* - acetylaminophenylethyl)amine, and 41 ml. of methyl ethyl ketone was heated to 65—80 C for one hour. After cooling the reaction mixture, the precipitate thus formed was filtered off and the filtrate was concentrated under a reduced pressure. The residue thus formed was dissolved in 40 ml. of ethanol at a temperature below 50° C. and the solution was allowed to stand at room temperature to crystallise. The crystals were recovered by filtration to give 3.7 g. of 4-benzyloxy-3-nitro-α-[N-benzyl-N-(1 - methyl - 2 - *p* - acetylaminophenylethyl)amino]acetophenone.

b). In 30 ml. of methanol was suspended 2.7 g. of 4-benzyloxy-3-nitro-α-[N-benzyl-N - (1 - methyl - 2 - *p* - acetylaminophenylethyl)amino]acetophenone and after adding to the suspension 0.6 g. of sodium borohydride under ice-cooling, the mixture was stirred for one hour. After adding water to the reaction mixture and distilling off methanol therefrom under a reduced pressure, the product was extracted with benzene. The extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated under a reduced pressure to give 2.6 g of yellowish powder of 4-benzyloxy-3-nitro-α-[N-benzyl-N - (1 - methyl - 2 - *p* - acetylaminophenylethyl)aminoethyl]benzyl alcohol.

c). In 20 ml of methanol was dissolved

1.3 g of 4 - benzyloxy - 3 - nitro - α - [N-benzyl - N -(1 - methyl - 2 - *p* - acetylaminophenylethyl)aminomethyl]benzyl alcohol and after adding to the solution 0.7 g of iron powder, 0.6 ml of 4.8 normal hydrochloric acid and 3 ml of water the mixture was refluxed for two hours and 30 minutes. After filtering off insoluble materials from the reaction mixture, 0.8 g of sodium carbonate was added and the mixture was stirred for 2 hours. The reaction mixture obtained was diluted with water, methanol was distilled off under reduced pressure and the residue was extracted with benzene. The extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give 1.1 g. of crystalline powder of 3-amino-4-benzyloxy-α-[N-benzyl-N - (1 - methyl - 2 - *p* - acetylaminophenylethyl)aminomethyl]benzyl alcohol.

d). In 6 ml. of 5:3 acetic anhydride-formic acid was dissolved 1.0 g. of 3 - amino - 4-benzyloxy - α - [N - benzyl - N - (1 - methyl - 2 - *p* - acetylaminophenylethyl)-aminomethyl]benzyl alcohol and after allowing to stand overnight, the reaction mixture was concentrated under a reduced pressure. The residue was dissolved in a mixture of 10 ml. of methanol and 2 ml. of water and after adding 0.5 g of potassium hydroxide to the solution, the mixture was stirred for one hour at room temperature. Methanol was distilled off under a reduced pressure, and the residue was mixed with water and extracted with benzene. Thereafter, the extract was washed with water, dried over anhydrous magnesium sulfate, and the solvent was distilled off therefrom to provide 0.9 g. of crystalline powder of 4-benzyloxy-3-formylamino-α - [N - benzyl - N - (1 - methyl - 2-*p* - acetylaminophenylethyl)aminomethyl]-benzyl alcohol.

Nuclear magnetic resonance spectrum-($CDCl_3$)

δ: 2.04 ppm (S, 3H, H of the methyl group of p-acetylamino group), 8.38 ppm (S, 1H, H of the formyl group), 4.4 ppm (m, 1H, H of the methine group at the root of hydroxyl group).

In the following reference preparations the same procedure as above was repeated using different starting materials.

A). By using 2.7 g. of 4-benzyloxy-3-nitro-α-bromoacetophenone and 4.8 g. of N-benzyl - N - (1 - methyl - 2 - {3,4,5 - trimethoxyphenyl}ethyl)amine as the starting materials, 1.2 g. of crystalline powder of 4-benzyloxy - 3 - formylamino - α - [N - benzyl-N - (1 - methyl - 2 - {3,4,5 - trimethoxyphenyl}ethyl)aminomethyl]benzyl alcohol was obtained.

Nuclear magnetic resonance spectrum ($CDCL_3$):

δ: 3.6 ppm., 3.7 ppm. (9H, H of the methyl group of 3,4,5 - trimethoxy group), 8.36 ppm. (S, 1H, H of formyl group), 4.46 ppm. (m, 1H, H of the methine group at the root of hydroxyl group.

B). By using 10.4 g. of 4-benzyloxy-3-nitro - α - bromoacetophenone and 15.2 g. of N - benzyl - N - (1 - methyl - 3 - *p*-hydroxyphenylpropyl)amine as the starting materials, 5.9 g. of 4-benzyloxy-3-formylamino - α [N - benzyl - N - (1 - methyl-3 - *p* - hydroxyphenylpropyl)aminomethyl]-benzyl alcohol was obtained.

Nuclear magnetic resonance spectrum ($CDCl_3$):

δ: 1.76 ppm. (m(2H, H of the methylene group at the 2-position of 3-*p*-hydroxyphenyl-propyl group), 8.38 (S, 1H, H of formyl group), 4.56 ppm. (m, 1H, H of the methine group at the root of hydroxyl group).

C). By using 6.75 g. of 4-benzyloxy-3-nitro-α-bromoacetophenone and 9.2 g. of N-benzyl - N - *p* - tolyl(isopropylamine as the starting materials, 3.7 g. of 3-formylamino-4-benzyloxy - α - [N - benzyl - N - (1 - methyl-2 - *p* - tolylethyl)aminomethyl]benzyl alcohol was obtained:

Nuclear magnetic resonance spectrum ($CDCl_3$):

δ: 2.30 ppm. (S, 3H,ø—CH_3), 5.02 ppm. (S, 2H, —OCH_2—).

D). By using 7.55 g. of 4-benzyloxy-3-nitro-α-bromoacetophenone and 11.6 g. of N-benzyl - N - (1 - ethyl - 2 - *p* - methoxyphenylethyl)amine as the starting materials, 1.5 g. of 3-formylamino-4-benzyloxy-α-[N-benzyl - N - (1 - ethyl - 2 - *p* - methoxyphenylethyl)aminomethyl]benzyl alcohol was obtained.

Elemental analysis for $C_{28}H_{30}N_2O_4$:

	C(%)	H(%)	N(%)
Calculated:	75.81	7.11	5.20
Found:	75.67	7.25	5.37

Reference Preparation 12.

a).

A mixture of 9.4 g. of 4-benzyloxy-3-nitro-α-bromoacetophenone and 13.7 g. of N-benzyl - N - (1 - methyl - 2 - *p* - methoxyphenylethyl)amine was heated together with 50 ml. of methyl ethyl ketone at 70—80° C. for one hour. After cooling the solution and filtering off the precipitate thus formed, the filtrate was concentrated under a reduced pressure and ethanol was added to the residue, whereby crystals formed. The crystals were recovered by filtration and recrystallized from ethanol to give 12.8 g. of 4-benzyloxy-3-nitro - α - [N - benzyl - N - (1 - methyl-2 - *p* - methoxyphenylethyl)amino]acetophenone melting point 100—102° C.

b).

In 200 ml. of ethanol was suspended 12.8 g. of 4-benzyloxy-3-nitro-α-[N-benzyl-N-(1-methyl - 2 - *p* - methoxyphenylethyl)amino]-acetophenone and after adding to the sus-

pension 1.8 g. of sodium borohydride, the mixture was stirred overnight. Ethanol was distilled off from the reaction product and after adding water to the residue, the product was extracted with benzene. The extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated under a reduced pressure to provide 10.7 g. of yellow oily 4 - benzyloxy - 3 - nitro - α - N - benzyl-N - (1 - methyl - 2 - *p* -methoxyphenylethyl)aminomethyl]benzyl alcohol.

c).

In 70 ml. of methanol was dissolved 10.7 g. of 4 - benzyloxy - 3 - nitro - α - [N-benzyl - N - (1 - methyl - 2 - *p* - methoxyphenylethyl)aminomethyl] - benzyl alcohol and after adding to the solution 15 ml. of 2.2 normal hydrochloric acid solution, 10 ml. of water, and 5.4 g. of iron powder, the mixture was refluxed for one hour. After filtering off insoluble material from the reaction mixture, the filtrate was concentrated under a reduced pressure, the residue was mixed with 50 ml. of benzene, 10 ml. of water, and 10 g. of sodium carbonate and then extracted with benzene. The extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated under a reduced pressure to give 8.8 g. of yellow caramel-like 3-amino-4-benzyloxy - α - N - benzyl - N - (1 - methyl-2 - *p* - methoxyphenylethyl)aminomethyl]-benzyl alcohol.

d).

In 20 ml. of 5 : 3 acetic anhydride-formic acid was dissolved 5.5 g. of 3-amino-4-benzyloxy - α - [N - benzyl - N - (1-methyl - 2 - *p* - methoxyphenylethyl)aminomethyl]benzyl alcohol and after allowing the solution to stand overnight at room temperature, the solution was concentrated under a reduced pressure. The residue was mixed with 50 ml. of methanol, 3 ml. of water, and 3.5 g. of sodium carbonate and the mixture was stirred for 2 hours at room temperature. Methanol was distilled off from the reaction product under a reduced pressure and the residue obtained was extracted with benzene. The extract was washed with water, dried over anhydrous magnesium sulfate, and then the solvent was distilled off to provide 5.1 g. of the crystalline powder of 4-benzyloxy-3-formylamino - α - [N - benzyl - N - (1-methyl - 2 - *p* - methoxyphenylethyl)aminomethyl]benzyl alcohol. 4.9 g. of this product was dissolved in 20 ml. of methanol and after adding to the solution 1 g. of fumaric acid, the mixture was concentrated under a reduced pressure. When the residue was dissolved in 80 ml. of ethyl acetate and the solution was allowed to stand overnight, crystals formed. The crystals were recovered by filtration and recrystallized from isopropanol to provide 3.2 g. of white crystals of 4-benzyloxy-3-formylamino - α - [N - benzyl - N - (1 - methyl-2 - *p* - methoxyphenylethyl)aminomethyl]-benzyl alcohol.1-fumarate melting point 173° C.

In 30 ml. of 90% methanol was suspended 3 g. of the product prepared above and after adding to the suspension 1.5 g. of sodium carbonate followed by stirring for 30 minutes, the mixture was concentrated under a reduced pressure. The residue was mixed with 10 ml. of water and extracted with 30 ml. of benzene. The extract was washed with water, dried over anhydrous magnesium sulfate, and then concentrated under a reduced pressure to give 2.3 g. of a white powder.

Nuclear magnetic resonance spectrum ($CDCl_3$):

δ: 4.52 ppm. (m, 1H, CH at the root of hydroxyl group), 3.48 ppm., 3.87 ppm. (AB type quartet, 2H, CH_2 at the root of N).

This product is called 4 - benzyloxy - 3-formylamino - α - [N - benzyl - N - (1-methyl - 2 - *p* - methoxyphenylethyl)aminomethyl]benzyl alcohol [A].

The solvent was distilled off from the mother liquor left after recovering the crystals of 4 - benzyloxy - 3 - formylamino - α-[N - benzyl - N - (1 - methyl - 2 - *p*-methoxyphenylethyl)aminomethyl]benzyl alcohol.1-fumarate [A] in the aforesaid step and the residue was dissolved in 30 ml. of methanol. After adding to the solution 3 ml. of water and 1.5 g. of sodium carbonate followed by stirring for 30 minutes, the mixture was concentrated under a reduced pressure. The residue was mixed with 10 ml. of water and extracted with benzene. The extract was washed with water, dried over anhydrous magnesium sulfate, and then the solvent was distilled off to provide 2.3 g. of the faint-brownish powder of 4 - benzyloxy - 3 -formylamino - α - [N - benzyl - N - (1 - methyl-2 - *p* - methoxyphenylethyl)aminomethyl]-benzyl alcohol. The product was subjected to a silica gel column chromatography and the eluate obtained using 10 : 1 benzene-ethyl acetate was concentrated under a reduced pressure to give a white powder.

Nuclear magnetic resonance spectrum ($CDCl_3$):

δ: 4.40 ppm. (m, 1H, CH at the root of hydroxyl group), 3.73 ppm. (S, 2H, CH_2 at the root of N).

This product is 4-benzyloxy-3-formylamino-α - [N - benzyl - N - (1 - methyl - 2 - *p*-methoxyphenyl)aminomethyl]benzyl alcohol [B].

Reference Procedure 13.

a).

A mixture of 2.7 g. of 4-benzyloxy-3-acetylamino - α - bromoacetophenone and 4.0 g. of N - benzyl - N - (1 - methyl - 2 - *p*-hydroxyphenylethyl)amine was stirred together with 80 ml. of methyl ethyl ketone at room temperature for 4 hours. After filtering off the precipitate thus formed, the filtrate was concentrated under a reduced pressure and

the residue obtained was subjected to a silica gel column chromatography using 10 : 2 benzene ethyl acetate mixture as the eluate to give 2.2 g. of yellowish crystalline powder of 4 - benzyloxy - 3 - acetylamino - α - [N-benzyl - N - (1 - methyl - 2 - *p* - hydroxyphenylethyl)amino]acetophenone.

b).

In 18 ml. of ethanol was dissolved 0.9 g. of 4 - benzyloxy - 3 - acetylamino - α - [N-benzyl - N - (1 - methyl - 2 - *p* - hydroxyphenylethyl)amino]acetophenone and after adding to the solution 0.1 g. of 10% palladium on carbon, the catalytic reduction was conducted at normal temperature and pressure until 78 ml. of hydrogen was absorbed. After filtering off the catalyst, the filtrate was concentrated under a reduced pressure and the residue obtained was subjected to a silica gel column chromatography. From the eluate recovered using 4 : 2 : 1 ethyl acetate-benzene-methanol mixture, 0.5 g. of the yellowish crystalline powder of 3 - acetylamino - 4-hydroxy - α - [N - (1 - methyl - 2 - *p*-hydroxyphenylethyl)amino]acetophenone was obtained.

Nuclear magnetic resonance spectrum: (D_6—DMSO)

δ: 2.12 ppm. (S, 3H, H of the methyl group of 3-acetylamino group), 0.98 ppm. (d, 3H, H of 1-methyl group), 4.10 ppm. (2H, H of the methylene group between carbonyl group and amino group).

Example 18.

In 12 ml. of ethanol was dissolved 1.2 g. of 4 - benzyloxy - 3 - acetylamino - α - [N-benzyl - N - (1 - methyl - 2 - *p* - hydroxyphenylethyl)aminomethyl]benzyl alcohol prepared in the Reference Preparation 8 and after adding to the solution 0.2 g. of 10% palladium on carbon, the catalytic reduction was conducted at normal temperature and pressure until 110 ml. of hydrogen had been absorbed. After filtering off the catalyst, the filtrate was concentrated under a reduced pressure to give 0.75 g. of crystalline powder of 3-acetylamino-4 - hydroxy - α - [N - (1 - methyl - 2 - *p*-hydroxyphenylethyl)aminomethyl]benzyl alcohol.

Elemental analysis for $C_{19}H_{24}N_2O_4$:

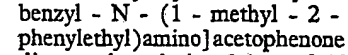
	C(%)	H(%)	N(%)
Calculated:	66.26	7.02	8.13
Found:	66.43	6.81	7.88

Example 19.

In 50 ml. of ethanol was dissolved 1.2 g. of the 3 - benzyloxyacetylamino - 4 - benzyloxy - α - [N - benzyl - N - (1 - methyl - 2-p - hydroxyphenylethyl)aminomethyl]benzyl alcohol and after adding to the solution 0.5 g. of 10% palladium or carbon, the catalytic reduction was conducted at normal temperature and pressure until 137 ml. of hydrogen had been absorbed. After filtering off the catalyst, the filtrate was concentrated under a reduced pressure to give 0.8 g. of white caramel-like 3 - hydroxyacetylamino - 4 - hydroxy - α - [N - (1 - methyl - 2 - *p* - hydroxyphenylethyl)aminomethyl]benzyl alcohol.

Nuclear magnetic resononce spectrum (D_6—DMSO):

δ: 0.90 ppm. (d, 3H, >CH—CH_3), 3.98 ppm.



(S, 2H, —C(=O)—CH_2O—).

4.50 ppm. (m, 1H, >CH—OH).

Example 20.

In 30 ml. of methanol was dissolved 800 mg. of 3 - (N - acetyl - β - alanyl)amino-4 - benzyloxy - α - [N - benzyl - N - (1-methyl - 2 - *p* - hydroxyphenylethyl)aminomethyl]benzyl alcohol prepared in the Reference Preparation 10 and after adding to the solution 50 mg. of 10% palladium on carbon, the catalytic reduction was conducted at normal temperature and pressure until 65 ml. of hydrogen had been absorbed. After filtering off the catalyst, the filtrate was concentrated under a reduced pressure to give 470 mg. of white caramel-like 3-(N-acetyl-β-alanyl)amino - 4 - hydroxy - α - [N - (1-methyl - 2 - *p* - hydroxyphenylethyl)aminomethyl]benzyl alcohol.

Nuclear magnetic resonance spectrum (D_6—DMSO):

δ: 0.90 ppm. (d, 3H, >$CHCH_3$), 1.80 ppm, (S, 3H, —$COCH_3$), 4.45 ppm.

(m, 1H, >CHOH).

Example 21.

In 7 ml. of ethanol was dissolved 0.7 g. of the 4 - benzyloxy - 3 - formylamino - α-[N - benzyl - N - (1 - methyl - 2 - *p* - acetylaminophenylethyl)aminomethyl]benzyl alcohol and after adding to the solution 0.15 g. of 10% palladium on carbon, the catalytic reduction was carried out at normal temperature and pressure until 61 ml. of hydrogen had been absorbed. After filtering off the catalyst, the filtrate was concentrated under a reduced pressure to give 0.34 g. of crystalline powder of 3-formylamino-4-hydroxy-α-[N - (1 - methyl - 2 - *p* - acetylaminophenylethyl)aminomethyl]benzyl alcohol.

Nuclear magnetic resonance spectrum (D_6—DMSO):

δ: 2.04 ppm. (S, 3H, H of the methyl group of *p* - acetylamino group), 8.30 ppm. (S, 1H, H of formyl group), 4.48 ppm. (m, 1H, H of the methine group at the root of hydroxyl group).

Example 22.

In 12 ml. of ethanol was dissolved 1.2 g.

of 4 - benzyloxy - 3 - formylamino - α - [N-benzyl - N - (1 - methyl - 2 - {3,4,5 - trimethoxyphenyl} - ethyl)aminomethyl]benzyl alcohol prepared in the Reference Example 11. After adding to the solution 0.2 g. of 10% palladium on carbon, the catalytic reduction was conducted until 110 ml. of hydrogen had been absorbed. The catalyst was then filtered off and the filtrate was concentrated under a reduced pressure to provide 0.7 g. of crystalline powder of 3 - formylamino - 4 - hydroxy - α - [N - (1 - methyl - 2 - {3,4,5 - trimethoxyphenyl}ethyl)aminomethyl]benzyl alcohol.

Elemental analysis for $C_{21}H_{28}N_2O_6$:

	C(%)	H(%)	N(%)
Calculated:	62.36	6.98	6.93
Found:	61.99	6.98	6.66

Example 23.

In 40 ml. of ethanol was dissolved 2.2 g. of 4 - benzyloxy - 3 - formylamino - α - [N-benzyl - N - (1 - methyl - 3 - *p* - hydroxyphenylpropyl)aminomethyl]benzyl alcohol prepared in the Reference Preparation 11 and after adding to the solution 0.3 g. of 10% palladium on carbon, the catalytic reduction was conducted at normal temperature and pressure until 195 ml. of hydrogen had been absorbed. After filtering off the catalyst, the filtrate was concentrated under a reduced pressure to give 1.3 g. of crystalline powder of 3 - formylamino - 4 - hydroxy - α - [N-(1 - methyl - 3 - *p* - hydroxyphenylpropyl)-aminomethyl]benzyl alcohol. When 0.60 g. of the product thus obtained and 0.102 g, of fumaric acid were dissolved in 95% ethanol and the solution was allowed to stand, white crystals formed, which were recovered by filtration to provide 0.55 g. of 3-formylamino-4 - hydroxy - α - [N - (1 - methyl - 3 - *p*-hydroxyphenylpropyl) - aminomethyl]benzyl. ½fumarate.monohydrate.

Elemental analysis for $C_{21}H_{28}N_2O_7$:

	C(%)	H(%)	N(%)
Calculated:	59.99	6.71	6.66
Found:	60.07	6.81	6.74

Example 24.

In 50 ml. of ethanol was dissolved 1.62 g. of 3 - formylamino - 4 - benzyloxy - α - [N-benzyl - N - (1 - methyl - 2 - *p* - tolylethyl)-aminomethyl]benzyl alcohol prepared in the Reference preparation 11 and after adding to the solution 0.3 g. of 10% palladium on carbon, the catalytic reduction was conducted at normal temperature and pressure until 154 ml. of hydrogen had been absorbed. The catalyst was filtered off and after adding to the remaining ethanol solution 8 ml. of water, and 186 mg. of fumaric acid, the solvent was removed from the resultant solution under a reduced pressure. The residue was dissolved in ethanol and benzene was added to the solution until the solution became slightly turbid. When the system was allowed to stand in a refrigerator, 550 mg. of white crystal formed. The crystals were recovered and recrystallized from ethanol-benzene to give 3-formylamino-4 - hydroxy - α - [N - (1 - methyl-2 - *p* - tolylethyl)aminomethyl]benzyl alcohol. ½fumarate.½hydrate, melting point 132—133° C. (decomposed).

Elemental analysis for $C_{21}H_{26}N_2O_5.\frac{1}{2}H_2O$:

	C(%)	H(%)	N(%)
Calculated:	63.78	6.88	7.08
Found:	63.99	6.70	6.82

Example 25.

In 10 ml. of ethanol was dissolved 200 mg. of 3 - formylamino - 4 - benzyloxy - α - [N-benzyl - N - (1 - ethyl - 2 - *p* - methoxyphenylethyl)aminomethyl]benzyl alcohol and after adding to the solution 50 mg. of 10% palladium on carbon, the catalytic reduction was conducted at normal temperature and pressure until 31 ml. of hydrogen had been absorbed. After filtering off the catalyst, the solvent was distilled off under a reduced pressure to give 100 mg. of white caramel-like 3 - formylamino - 4 - hydroxy - α[N-(1 - ethyl - 2 - *p* - methoxyphenylethyl)-aminomethyl]benzyl alcohol.

Nuclear magnetic resonance spectrum (D_6—DMSO):

δ: 0.85 ppm. (3H, —CH_2CH_3), 1.25 ppm (2H, —CH_2CH_3), 4.47 ppm.

(1H, —CHOH), 8.31 ppm. (1H, —CH).

Example 26.

In 10 ml. of ethanol was dissolved 0.52 g. of the 3 - formylamino - 4 - benzyloxy - α-[N - benzyl - N - (1 - methyl - 2 - *p*-methoxyphenylethyl)aminomethyl]benzyl alcohol [A] prepared in the Reference preparation 12 d) and after adding to the solution 0.2 g. of 10% palladium on carbon, the catalytic reduction was conducted at normal temperature and pressure until 48 ml. of hydrogen had been absorbed. After filtering off the catalyst, the filtrate was concentrated under a reduced pressure to give 0.35 g. of white crystalline powder of 3-formylamino-4-hydroxy - α - [N - (1 - methyl - 2 - *p*-methoxyphenylethyl)aminomethyl]benzyl alcohol [A]. When 0.35 g. of this product was dissolved in 7 ml. of 95% ethanol together with 0.06 g. of fumaric acid and the solution was allowed to stand, crystals formed. The crystals were recovered by filtration to provide 0.34 g. of white crystals of 3-formylamino - 4 - hydroxy - α - [N - (1 - methyl-2 - *p* - methoxyphenylethyl)aminomethyl]-benzyl alcohol [A].½fumarate, melting point 138—140° C. (decomposed).

Elemental analysis for $C_{21}H_{26}N_2O_6.H_2O$:

	C(%)	H(%)	N(%)
Calculated:	59.99	6.71	6.66
Found:	59.63	6.65	6.71

Example 27.

In 30 ml. of ethanol was dissolved 0.79 g. of 3 - formylamino - 4 - benzyloxy - α - [N-benzyl - N - (1 - methyl - 2 - *p* - methoxyphenylethyl)aminomethyl]benzyl alcohol [B] prepared in the Reference Preparation 12-d) and after adding to the solution 0.2 g. of 10% palladium on carbon, the catalytic reduction was conducted at normal temperature and pressure until 73 ml. of hydrogen had been absorbed. After filtering off the catalyst, the filtrate was concentrated under a reduced pressure to give 0.57 g. of white powder of 3 - formylamino - 4 - hydroxy - α - [N-(1 - methyl - 2 - *p* - methoxyphenylethyl)-aminomethyl]benzyl alcohol [B]. 0.57 g. of this product was dissolved in 8 ml. of 95% ethanol together with 0.087 g. of fumaric acid and after adding to the solution 0.5 ml. of water, the resulting solution was allowed to stand, when white crystals formed. The crystals were recovered by filtration to provide 0.3 g. of 3-formylamino-4-hydroxy-α-[N - (1 - methyl - 2 - *p* - methoxyphenylethyl)aminomethyl]benzyl alcohol [B]. ½fumarate, melting point 154—155° C. (decomposed).

Elemental analysis for $C_{21}H_{26}N_2O_6 \cdot \frac{2}{3} H_2O$

	C(%)	H(%)	N(%)
Calculated:	60.89	6.65	6.76
Found:	60.94	6.69	6.77

Example 28.

In 3.5 ml. of ethanol was dissolved 0.28 g. of 3 - acetylamino - 4 - hydroxy - α - [N-(1 - methyl - 2 - *p* - hydroxyphenylethyl)-amino]acetophenone and after adding to the solution 0.16 g. of 10% palladium on carbon, the catalytic reduction was conducted at normal temperature and pressure until 20 ml. of hydrogen had been absorbed. After filtering off the catalyst, the filtrate was concentrated under a reduced pressure to give 0.21 g. of crystalline powder of 3-acetylamino-4 - hydroxy - α - [N - (1 - methyl - 2 - *p*-hydroxyphenylethyl)aminomethyl]benzyl alcohol.

The product thus obtained coincided with the product obtained in the Example 18 in infrared absorption spectra.

Example 29 (Tablet).

Formula:

3-Acetamido-4-hydroxy-α-(isopropylaminomethyl)-benzyl alcohol ½ fumarate	100 mg.
Lactose	100.0 g.
Starch	35.0 g.
Talc	5.0 g.

From the above formula 1,000 tablets were prepared. Each tablet had a diameter of 7 mm. and if necessary they may be coated.

Example 30 (Injection).

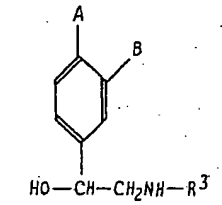
Formula:

3-Acetamido-4-hydroxy-α-(isopropylaminomethyl)-benzyl alcohol ½fumarate	50 mg.
Sodium chloride	8.5 g.
Citric acid	1.0 g.
Water to make	1,000 ml.
	pH 4.0—6.0

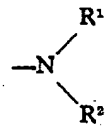
From the above formula 1,000 injection ampoules each containing 1 ml. were prepared. The injection was prepared by dissolving the above solid components in the water, sterilizing by filtration, and pouring in a ampoule followed by sealing.

WHAT WE CLAIM IS:—

1. An α-aminomethylbenzyl alcohol represented by the general formula

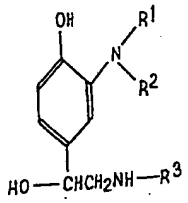


wherein one of A and B represents a hydrogen atom or a hydroxyl group while the other represents



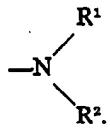
(wherein R^1, which is different from R^2, represents a hydrogen atom or an alkyl group and R^2 represents a hydrogen atom or a —CO—R^4 group, in which R^4 represents a hydrogen atom or an alkyl group which may be substituted by a hydroxyl group, an alkoxyl group, or an acylamino group), and R^3 represents an alkyl group other than a methyl group or a phenyl alkyl group which may be substituted by a hydroxyl group, an alkyl group, an alkoxyl group, or an acylamino group; and pharmacologically acceptable addition salts thereof.

2. An α-aminomethylbenzyl alcohol as claimed in Claim 1 wherein said alcohol is a 3 - amino - 4 - hydroxy - α - aminomethylbenzyl alcohol represented by the general formula



wherein R^1, R^2 and R^3 are as defined in claim 1.

3. An α - aminomethylbenzyl alcohol as claimed in Claim 1 wherein one of said A and B is hydrogen and the other is



4. 3 - formamido - 4 - hydroxy - α - [N-(1 - methyl - 2 - *p* - hydroxyphenylethyl)-aminomethyl]benzyl alcohol.

5. 3 - formamido - 4 - hydroxy - α - [N-(1 - methyl - 2 - *p* - methoxyphenylethyl)-aminomethyl]benzyl alcohol.

6. 3 - formamido - 4 - hydroxy - α - *t*-butylaminomethylbenzyl alcohol.

7. 4 - hydroxy - 3 - methylamino - α - *t*-butylaminomethylbenzyl alcohol.

8. A method of making an α-aminomethylbenzyl alcohol as claimed in Claim 1 substantially as described in any of Examples 1 to 28 herein.

9. An α - aminomethylbenzyl alcohol prepared by a method according to Claim 8.

10. A pharmaceutical composition comprising an α-aminomethylbenzyl alcohol as claimed in any of Claims 1 to 7 or 9 as active ingredient together with a pharmaceutically acceptable diluent or medium.

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